REMARKS

Status of the Claims

Claims 1-2, 4-8, 10-50 and 52-79 are currently pending in the application.

Claim 54 is cancelled without prejudice or disclaimer with entry of the above amendment.

Claims 32-40, 52-53 and 65-67 were previously withdrawn by the Office.

Claims 1-2, 4-8, 10-31, 41-50, 55-64 and 68-79 remain under consideration with entry of this Response.

Summary

Claims 1-2, 4-8, 10-50 and 52-79 are pending in the application and were examined in the Office Action dated 25 June 2009. Applicants note with appreciation that the following claim rejections have been withdrawn by the Office: **(1)** the rejection of claims 1, 2, 4-6, 10-13, 17, 18, 23-30, 46-50, 54, 55, 57, 70, 71 and 76-78 under 35 U.S.C. §102(b) as anticipated by U.S. Patent No. 5,747,058 to Tipton et al. ("Tipton"); **(2)** the rejection of claims 7, 8, 14-16, 19-22, 41-45, 58-62, 68-71, 73-76 and 79 under 35 U.S.C. §103(a) as unpatentable over Tipton; and **(3)** the rejection of claims 31, 63, 64 and 72 under 35 U.S.C. §103(a) as unpatentable over Tipton. However, the following new grounds of rejection have been asserted: **(a)** claim 54 stands rejected under 35 U.S.C. §112, second paragraph as indefinite; and **(b)** claims 1, 2, 4-8, 10-50 and 52-78 stand rejected under 35 U.S.C. §103(a) as unpatentable over Tipton. Applicants respectfully traverse all pending claim rejections for the following reasons.

Overview of the Amendment

Applicants, by way of the above claim amendment, have cancelled claim 54 without prejudice or disclaimer. Cancellation of this claim is not in acquiescence to any asserted rejection, and applicants expressly reserve their right to bring the claim again in another related application.

Clarification of Claims Status

Claim 54 was incorrectly indicated as being amended in the comments section of the Response dated 13 May 2009 that accompanied the Request for Continued Examination of that same date. Applicants confirm that claim 54 was not "currently amended" in that response.

In the Office Action dated 25 June 2009, the Office has indicated that claims 32-40, 52, 53, and 65-67 stand rejected under 35 U.S.C. §103(a) (see current Office Action at page 3, paragraph 7); however, those claims were expressly withdrawn from consideration by the Office (see Office Action dated 11 September 2007, page 1), and are likewise indicated as still being withdrawn from consideration in the current Office Action at page 1. Clarification of the status of claims 32-40, 52, 53 and 65-67 is thus respectfully requested.

Claim 56 is indicated as withdrawn from consideration and free from any ground of rejection at page 1 of the current Office Action; however, claim 56 has been indicated to stand rejected under 35 U.S.C. §103(a) (see current Office Action at page 3, paragraph 7). In addition, the amendment to claim 56 submitted with the Response dated 13 May 2009 appears to have been entered. Clarification of the status of claim 56 is thus respectfully requested.

Claim 79 has been indicated to stand rejected at page 1 of the current Office Action; however, no pending ground of rejection has been asserted against that claim (see page 3, paragraphs 3 and 7 of the current Office Action). Clarification of the status of claim 79 is thus respectfully requested.

The Rejection under 35 U.S.C. §112, Second Paragraph

Claim 54 stands rejected under 35 U.S.C. §112, second paragraph, as indefinite. Applicants respectfully submit that the metes and bounds of claim 54 are clear in view of the specification as filed. However, solely in the interest of expediting prosecution of the instant application, applicants have cancelled claim 54 rendering the instant ground of

rejection moot. Reconsideration and withdrawal of the rejection is thus respectfully requested.

The Rejection under 35 U.S.C. §103(a)

Claims 1, 2, 4-8, 10-50 and 52-78 have been indicated to stand rejected under 35 U.S.C. §103(a) as obvious over Tipton. Applicants respectfully traverse the rejection for the following reasons.

In pertinent part, 35 U.S.C. §103 provides that a patent may not be obtained "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious to a person having ordinary skill in the art." 35 U.S.C. §103. Any analysis under Section 103 must consider the following factual inquiries: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed subject matter and the prior art; and (4) secondary considerations of non-obviousness (such as commercial success and long-felt but unsolved need, failure of others, and unexpected results). *Graham v. John Deere Co.*, 383 U.S. 1, 17-18, (1966) (the "*Graham* factors"). The Supreme Court, in *KSR Intern. Co. v. Teleflex, Inc.*, 127 S. Ct. 1727 (2007) reaffirmed that the *Graham* factors "continue to define the inquiry that controls" an obviousness analysis. Furthermore, when considering the above-noted Graham factors, the Office must adhere to the following rules: (a) the claimed invention must be considered as a whole; (b) the references must be considered as a whole; (c) the references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention; and (d) reasonable expectation of success is the standard with which obviousness is determined. *Hodosh v. Block Drug Co., Inc.*, 229 USPQ 182, 187 n.5 (Fed. Cir. 1986).

(A) The claimed invention must be considered as a whole.

Applicants have disclosed and claimed a unique set of pharmaceutical formulation chemistries that provide unexpected and beneficial performance characteristics. More particularly, applicants have discovered for the first time that a particular set of

pharmaceutical excipients can be combined to provide an oral, controlled release pharmaceutical formulation suitable to provide for long term delivery (e.g., between 1-20 hours or greater) of potent and potentially dangerous drugs, where the subject formulations are also able to resist unwanted extraction of the entire drug dose as a result of simple extraction techniques such as those that can be performed using common solvents including water or ethanol. See Paragraphs [0045], [0049], [0059] and [0062] of the Published Specification. Applicants' oral formulations, and drug delivery devices containing such formulations, are therefore both safe and efficacious. The formulations are efficacious since they allow for the desirable benefit of sustained drug release, with favorable drug-release kinetics, during transit through the gastro-intestinal when taken as intended – thereby decreasing the number of times that a drug must be administered over the course of a day; and the formulations are safe since they are less susceptible to abuse than prior art tablet and capsule dosage forms, in particular they are resistant to extraction into water or ethanol solvents. See Paragraphs [0070], [0077]-[0083] of the Published Specification.

Accordingly, in claim 1, applicants have recited and claimed a specific invention that has the following express elements: (a) an oral dosage form; (b) containing a formulation that forms a network within the formulation and an outer surface when contacted with an aqueous environment; (c) the formulation includes a drug; (d) the formulation includes a HVLCM; (e) the formulation includes a network former; (f) the formulation includes a rheology modifier; and (g) the formulation includes a solvent. Claims 2, 4-8, 10-50, 52-53, and 55-60 each depend, either directly or indirectly from claim 1 and thus also contain the express combination of these same 7 basic elements.

Claim 70 recites a specific invention that has the following express elements: (a) an oral dosage form; (b) containing a formulation; (c) the formulation includes a drug; (d) the formulation includes a HVLCM; (e) the formulation includes a network former; (f) the formulation includes a rheology modifier; (g) the formulation includes a solvent; and (h) each of the elements (c)-(g) are present in sufficient amounts to (i) reduce the rate of extraction of the drug from the formulation with solvent, while (j) simultaneously providing desirable release kinetics of the drug upon administration to a subject. Claims

71-76 each depend either directly or indirectly from claim 70 and thus also contain the express combination of these same 10 basic elements.

Claim 77 recites a specific invention that has the following 3 express elements: (a) a drug delivery device; (b) comprising a formulation; (c) where the formulation forms a network within the formulation and an outer surface of the formulation upon exposure to an aqueous environment.

Claim 78 recites a specific invention that has the following 7 express elements: (a) a drug delivery device; (b) comprising a formulation; (c) the formulation includes a HVLCM; (d) the formulation includes a network former; (e) the formulation includes a rheology modifier; (f) the formulation includes a solvent; and (g) the formulation includes a drug.

Claim 79 recites a specific invention that has the following 7 express elements: (a) a drug delivery device; (b) comprising a formulation; (c) the formulation includes sucrose acetate isobutyrate (SAIB); (d) the formulation includes cellulose acetate butyrate (CAB); (e) the formulation includes isopropyl myristate (IPM); (f) the formulation includes ethyl lactate (EL); and (g) the formulation includes an opioid.

(B) The Tipton reference must be considered as a whole.

The Office has rejected claims 1, 2, 4-8, 10-50 and 52-78 as obvious over Tipton on the basis that "Tipton discloses a composition comprising HVLCM with sucrose acetate isobutyrate specifically employed" and further that Tipton provides a series of lists of additional excipients such as surfactants (col. 11, lines 40-67) "that meet network former of the claims"; oily components (col. 12, lines 18-45) "meeting the rheology modifier"; solvents (col. 2, lines 49-50 and col. 12, line 51); and "additives such as preservatives, antioxidants, stabilizers, vitamins", and finally that "the formulation of Tipton can be placed in gelatin capsules for oral administration (claim 88)." Office Action at page 4, first paragraph. The Office then concludes "the composition of Tipton would inherently possess the characteristics" of applicants' recited invention. Applicants respectfully submit that this conclusion is not a fair reading of the Tipton reference when considered as a whole. In particular:

(1) Tipton does not disclose applicants' recited combinations;

The Office has acknowledged that "Tipton does not disclose one composition that has HVLCM, CAB, solvent, and rheology modifier." Office Action at page 5, second paragraph. In other words, Tipton fails to disclose applicants' expressly recited combinations.

(2) Tipton does not disclose formulations having applicants' recited properties; and

The Office has failed to identify any relevant disclosure from Tipton that a particular disclosed oral formulation would provide for both desirable sustained release when taken properly but resist extraction into solvents such as water and ethanol, either inherently or expressly. The Office has merely asserted that "Tipton teaches HVLCMs, drugs, solvents and additives are formulated and that the additives are added as desired to modify the properties." Office Action at page 5, second paragraph. Applicants respectfully ask just what are "the properties" that the Office believes Tipton teaches one to modify? The Office has provided no technical or scientific basis whatsoever for the assertion that Tipton teaches formulations with applicants' express properties , and in particular has not provided any basis from Tipton for the assertion that any formulation fairly taught or suggested by Tipton would necessarily have applicants' recited properties.

(3) Tipton does not disclose the problem that applicants sought to solve.

Applicants set out to provide a much safer dosage form that those available in the prior art. In particular, applicants sought to create an oral formulation that would provide for both desirable sustained release when taken properly but resist extraction into solvents such as water and ethanol. The Office has failed to identify any disclosure whatsoever from Tipton that would identify the problem that applicants sought to solve. In fact, the Office has failed to identify any teaching, suggestion, motivation or inspiration from Tipton that would have led the skilled person to identify applicants' problem, and much less any such teaching, suggestion, motivation or inspiration that would have provided even a starting point for one to begin with Tipton and somehow arrive at

applicants' recited formulations, having applicants' recited properties, and solving applicants' particular problem.

Accordingly, when the Tipton reference is considered as a whole, it is clear that the reference does not disclose applicants' recited combinations. In addition, it is clear that Tipton further does not disclose formulations having applicants' recited properties, nor does Tipton even disclose the particular problem that applicants sought to solve with their unique and novel compositions.

(C) The Office has construed Tipton using impermissible hindsight vision afforded by the claimed invention.

At page 5 of the Office Action, first paragraph, the Office has attempted to reconstruct applicants' recited combination by picking and choosing elements from a series of unrelated "laundry lists" of optional additives that Tipton teaches can be employed in a composition containing a HVLCM. See Tipton, col. 9, lines 1-6. However, as established directly above, the Tipton reference does not disclose applicants' recited combinations, does not disclose formulations having applicants' recited properties, nor does Tipton even disclose the particular problem that applicants sought to solve with their unique and novel compositions. In addition, as established directly below, the skilled person cannot have had a reasonable expectation for success for providing any formulation having applicants' unique combination of properties, much less applicants' specifically recited formulations containing their unique combinations of pharmaceutical ingredients.

In order to meet its burden in establishing a rejection under 35 U.S.C. §103 the Office must first demonstrate that the cited art teaches or suggests all the claimed limitations. *See Pharmastem Therapeutics, Inc. v. Viacell, Inc.*, 491 F.3d 1342 (Fed. Cir. 2007). Furthermore, as indicated by the Supreme Court in *KSR Int'l Co. v. Teleflex Inc.*, in order to avoid pitfalls such as impermissible hindsight reconstruction, it will often be necessary "to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue." *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1740 (2007). In regard to applicants' recited invention, the Office has failed

to provide any showing from Tipton that there would have been an apparent reason to make applicants' specific combination of pharmaceutical ingredients. The Office has likewise failed to provide any showing from Tipton that a formulation could even be provided having applicants' unique set of performance characteristics. In fact, applicants' recited compositions would have been considered to be technically unattainable by the skilled person.

Accordingly, the Office has had to pick and choose from numerous different possible choices from each of several, unconnected lists of ingredients from Tipton in its attempt to possibly arrive at applicants' express combination. However, Tipton simply fails to indicate which particular choices are critical, and provides no guidance as to which of many possible combinations and/or choices from these unrelated lists are likely to be successful. The only possible way to navigate the course for the Office's picking and choosing from the Tipton reference is to use applicants' specification as a road-map in an impermissible hindsight reconstruction of applicants' recited invention. In such cases, where one can only "vary all parameters or try each of numerous possible choices until one possibly arrive[s] at a successful result, where the prior art [gives] either no indication of which parameters [are] critical or no direction as to which of many possible choices is likely to be successful" (*In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988), the finder of fact "should not succumb to hindsight claims of obviousness." *In re Kubin*, _ F.3d _, No. 2008-1184, slip op. at 14 (Fed. Cir. 2009).

(D) The Office has failed to show that there would have been a reasonable expectation of success for applicants' recited formulations.

As discussed herein above, applicants set out to provide a much safer dosage form than those available in the prior art and, specifically, applicants sought to develop an oral formulation that would provide for both desirable sustained release when taken properly but resist extraction into solvents such as water and ethanol. This was a conundrum. In order to have an efficacious sustained release oral dosage form, the formulation must allow for ready extraction of the drug at a desired level over time simply by passage through the digestive system. However, in order to have a safer sustained release dosage

form that resists extraction into solvents such as water and ethanol, the formulation must be highly resistant to extraction of the drug in aqueous or other liquid environments substantially identical to those encountered in the digestive system, such as in water or ethanol environments.

At the time of applicants' invention, the skilled person understood that controlled release dosage forms could be formulated to provide for sustained release of a drug after oral administration. However, the skilled person also understood that the controlled release mechanism of such prior art dosage forms could easily be defeated to release substantially all of an 8, 12 or 24 hour drug dose using simple water or ethanol extraction techniques. This was the necessary trade-off in formulating an efficacious oral dosage form that would provide for desired sustained delivery from the aqueous environment of the digestive tract – that is, the drug would also have to be susceptible to extraction using aqueous solvents. Accordingly, such prior art oral dosage forms were efficacious, but inherently unsafe since, especially for highly potent drugs with dangerous side effects, the ability to have immediate access to an entire 8, 12 or 24 hour drug dosage imperiled drug abusers with potential overdose or even death.

The same skilled person also understood the excellent solvent properties of both water and ethanol. Accordingly, one could presumably have formulated a controlled release oral dosage form that would be highly resistant to extraction of the drug from the controlled release matrix using solvents such as water or ethanol. Such a dosage form would be safer, that is, it would be resistant to common forms of abuse. However, that same dosage form would not be efficacious since it would not be expected to release the drug at any appreciable amount when taken as intended on the basis that the drug would be too tightly bound by the controlled release matrix. This was the expected trade-off in formulating a safer oral dosage form that would be highly resistant to extraction using aqueous solvents – that is, the dosage form could not be expected to provide for desired sustained delivery from the aqueous environment of the digestive tract, and would therefore be inoperable.

This means that, at the time of applicants' invention, the skilled person would not have expected that an oral formulation could provide for both desirable sustained release

when taken properly and sufficient resistance to extraction into solvents such as water and ethanol. Manipulations to a formulation to enhance efficacy and provide for desired sustained release properties when taken properly would have been expected to frustrate any abuse-resistant features of that formulation. In like manner, manipulations to a formulation to enhance abuse-resistance by extraction into water or ethanol would have been expected to frustrate the desired sustained release properties of that formulation, rendering it non-efficacious. Accordingly, applicants' novel formulations, which are based upon their unique combination of pharmaceutical ingredients and provide both desirable sustained release when taken properly and resist extraction into solvents such as water and ethanol, were simply unexpected. There cannot have been a reasonable expectation for success for an invention that would have been considered technically unattainable by the skilled person.

Applicants have demonstrated that their recited oral formulations provide desired sustained release pharmacokinetics (the formulations are efficacious when administered as intended). See Paragraphs [0132]-[0136] and Figure 5 from the Published Specification. Applicants have further demonstrated that their recited oral formulations are safer than prior art formulations since they resist extraction into water, whereas a prior art controlled release dosage form allowed for 100% extraction (see Paragraph [0130] of the Published Specification), and applicants have demonstrated that their recited oral formulations also resist extraction into ethanol whereas a prior art controlled release dosage form allowed for 100% extraction (see Paragraphs [0120]-[0129] and Figures 1-4 and 11 of the Published Specification). Providing such test data showing that a claimed composition possess unexpectedly improved properties or properties that the prior art does not have is strong evidence of non-obviousness. *In re Dillon*, 919 F.2d 688, 692-93 (Fed. Cir. 1990).

(E) The proper consideration of the Graham factual inquiries demonstrates that the Office has failed to establish a prima facie showing of obviousness over Tipton.

In order to establish a *prima facie* showing of obviousness, the Office must show by clear and convincing evidence that a person of ordinary skill in the art would have had

reason to attempt to make the specific composition recited in applicants' claims, having applicants' unique performance characteristics, and would have had a reasonable expectation of success in doing so. Applicants respectfully submit that the Office has failed to meet its' burden. In particular, when one considers the first Graham factual inquiry (the scope and content of the prior art), it is clear that Tipton, when that reference is considered as a whole, simply fails to disclose applicants' recited combinations. In addition, it is clear that Tipton fails to disclose formulations having applicants' recited properties, and Tipton even fails to disclose the particular problem that applicants sought to solve with their unique and novel compositions. Furthermore, when one considers the problem that applicants actually solved, it is clear that the skilled person would not have expected that such a formulation could even be developed.

When one considers the second Graham factual inquiry (the level of ordinary skill in the art), applicants submit that although the level of skill in the pharmaceutical arts is typically high, the technical hurdle that faced that skilled person was actually higher. The technical dogma at the time of applicants' invention was that an oral formulation simply could not provide for both desirable sustained release when taken properly, and resist extraction into solvents such as water and ethanol. Manipulations to a formulation to enhance efficacy and provide for desired sustained release properties when taken properly would have been expected to frustrate any abuse-resistant features of that formulation. In like manner, manipulations to a formulation to enhance abuse-resistance by extraction into water or ethanol would have been expected to frustrate the desired sustained release properties of that formulation, rendering it non-efficacious and thus inoperable.

When one considers the third Graham factual inquiry (the differences between the claimed subject matter and the prior art), applicants have shown by numerous working examples that their recited formulations possess the unique combination of performance features that provide for an efficacious sustained release oral dosage formulation that is also abuse-resistant. This result was unexpected from the prior art.

Finally, when one considers the fourth Graham factual inquiry (secondary considerations of non-obviousness such as commercial success and long-felt but unsolved

need, failure of others, and unexpected results), applicants' unique combination of pharmaceutical ingredients provides for considerably safer oral dosage forms that are also efficacious and provide desired sustained release performance. This result was unexpected from the prior art. In addition, the provision of such a safer dosage form has satisfied a long-felt, but unsolved need. Controlled release dosage forms containing highly unsafe and potentially abusable drugs have been commercially available for years prior to applicants' invention. However, such dosage forms fail to resist common forms of abuse such as extraction into common solvents including water and ethanol. As noted by the Federal Circuit, the presence of secondary considerations such as long-felt but unsolved need, failure of others and unexpected results "may often be the most probative and cogent evidence [of non-obviousness] in the record." *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538 (Fed. Cir. 1983).

Accordingly, for all of the foregoing reasons, the Office has failed to establish a *prima facie* case of obviousness over Tipton since the Office fails to show by clear and convincing evidence that a person of ordinary skill in the art would have had reason to attempt to make the specific composition recited in applicants' claims, having applicants' unique performance characteristics, and would have had a reasonable expectation of success in doing so. Accordingly, applicants respectfully submit that the rejection of claims 1, 2, 4-8, 10-50 and 52-78 under 35 U.S.C. §103(a) as obvious over Tipton is improper. Reconsideration and withdrawal of the rejection is thus earnestly solicited.

CONCLUSION

Applicants submit that the pending claims define an invention that is both novel and nonobvious over the cited art, and thus all claims are in condition for allowance. Acknowledgement of this by the Office in the form of an early allowance is thus respectfully requested. In addition, if the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, applicants invite the Examiner to contact the undersigned at (408) 777-4915.

The appropriate fee is either attached or authorized. If the Commissioner determines that an additional fee is necessary, the Commissioner is hereby authorized to charge any additional fees associated with this communication or credit any overpayment to Deposit Account No. **50-1953.**

Respectfully submitted,

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